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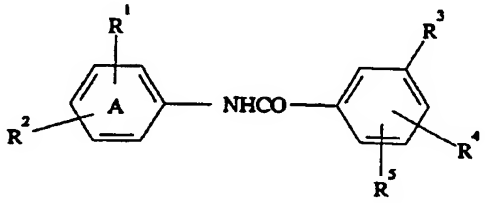
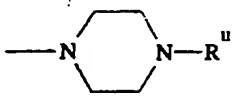
(54) **Benzanilide derivatives**

(57) Compounds of the general formula (I):-



(I)

and salts and solvates (eg hydrates) thereof, in which
R^1 represents H, F, Cl, Br, I, C_{1-6}alkyl or C_{1-6}alkoxy;
R^2 represents an optionally substituted phenyl or pyridyl group;
R^3 represents the group



(where R^{11} is H or C_{1-6}alkyl);
and R^3 and R^4 are optional standard substituents; are useful in the treatment of depression and other CNS disorders, being 5-HT_{1D} antagonists.

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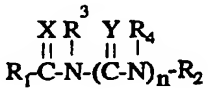
BENZANILIDE DERIVATIVES

This invention relates to novel benzanilide derivatives, to processes for their preparation, and to pharmaceutical compositions containing them.

European patent application number 0324521 discloses compounds of formula :



wherein
R_1 is *inter alia* a substituted phenyl group;
R_2 is *inter alia* a substituted phenyl group;
R_3 is *inter alia* H;
X is *inter alia* O; and
n is *inter alia* zero.

The compounds are said to be useful for the treatment of haematopoietic diseases. There is no disclosure of compounds wherein either of the phenyl rings R_1 or R_2 is substituted by an optionally substituted phenyl or pyridyl group.

Benzanilide derivatives which lack the phenyl substitution characteristic of the compounds of the present invention are also disclosed in European patent application no. 0310370. The compounds are said to have utility to anti-allgeric and anti-inflammatory agents.

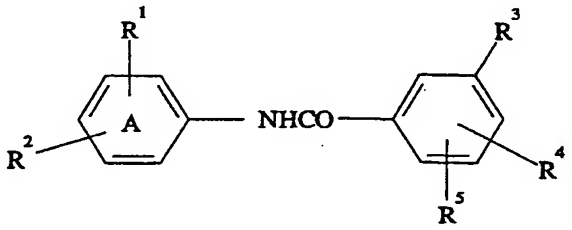
British patent specification no. 1157586 discloses the preparation of anti-bacterial compounds of formula:

$$R_2\text{-CONH-}R_3$$

wherein R_2 and R_3 each represents an optionally substituted aryl group. There is no suggestion of the particular substituted phenyl moieties of the compounds of the present invention.

Further benzanilide derivatives are disclosed in International patent application no. WO84/00545 as anti-arrhythmic and anti-malarial agents. There is no suggestion of the substitution pattern characteristic of the presently claimed compounds.

According to the invention we provide compounds of the general formula (I) :-



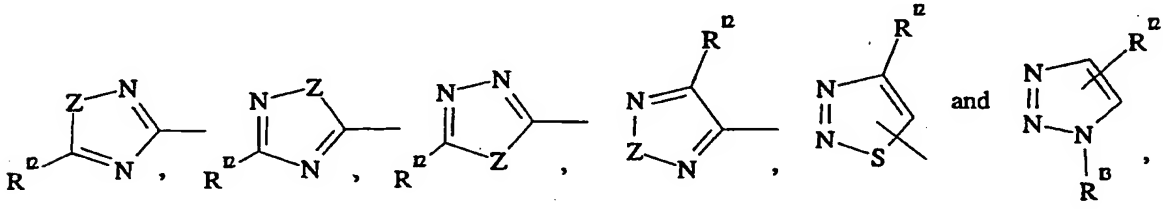
(I)

and salts and solvates (eg hydrates) thereof, in which

R^1 represents H, F, Cl, Br, I, C_{1-6}alkyl or C_{1-6}alkoxy;

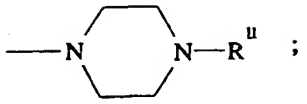
R^2 represents a phenyl or pyridyl group optionally substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkyl (optionally substituted by hydroxy), C_{1-6}alkoxy, hydroxy, $-CF_3$, -CN, $-NO_2$, $-CO_2R^{10}$, $-COR^6$, $-SR^6$, $-SOR^6$, $-SO_2R^6$, $-CR^6{=}NOR^7$, $-CONR^6R^7$, $-CONR^6(CH_2)_mCO_2R^7$, $-CONR^6(CH_2)_mOC_{1-4}$alkyl, $-SO_2NR^6R^7$, $-OC(O)NR^6R^7$, $-(CH_2)_nNR^8R^9$, $-(CH_2)_nOC(O)C_{1-4}$alkyl or C_{1-4}alkoxyalkyl (optionally substituted by C_{1-4}alkoxy or hydroxy); or

R^2 represents a phenyl group substituted by a group selected from



and optionally further substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy and C_{1-6}alkyl ;

R^3 represents the group



R^4 and R^5, which may be the same or different, each independently represent H, F, Cl, Br, I, hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl;
R^6, R^7 and R^8, which may be the same or different, each independently represent H or C_{1-6}alkyl ;
or $-NR^6R^7$ forms a saturated heterocyclic ring which has 4, 5 or 6 ring members, and optionally contains in the ring one oxygen or sulphur atom;
R^9 represents H, C_{1-6}alkyl, $-COR^{16}$ or $-SO_2R^{17}$;
or $-NR^8R^9$ forms a saturated heterocyclic ring which has 4, 5 or 6 ring members and optionally contains in the ring one oxygen or sulphur atom and may optionally be substituted by an oxo group;
R^{10} represents H, or C_{1-6}alkyl optionally substituted by one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy or $-NR^6R^7$;
R^{12} represents H, $-NR^{14}R^{15}$ or a C_{1-6}alkyl group optionally substituted by one or two substituents selected from C_{1-6}alkoxy, hydroxy and C_{1-6}acyloxy;
R^{11}, R^{13} and R^{14}, which may be the same or different, each independently represent H, or C_{1-6}alkyl;
R^{15} represents H C_{1-6}alkyl, C_{1-6}acyl, benzoyl or $-SO_2R^{18}$;
R^{16} represents H, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-4}alkoxyalkyl;
R^{17} represents C_{1-6}alkyl or phenyl;
R^{18} represents C_{1-6}alkyl or phenyl ;
Z represents an oxygen atom or a group selected from NR^{13} and $S(O)_k$; and
k represents zero, 1 or 2.

It is to be understood that the present invention encompasses all geometric and optical isomers of the compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

Salts of the compounds of formula (I) will preferably be pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic

acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicyclic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4+ (where R is C_{1-4}alkyl) salts.

In the compounds of general formula (I), the term 'C_{1-6}alkyl' or 'C_{1-6}alkoxy' as a group or part of a group means that the group is straight or branched and consists of 1 to 6 carbon atoms. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

In the compounds of general formula (I), the term 'acyl' as a group or part of a group means an alkanoyl group such as acetyl or pivaloyl.

When $-NR^6R^7$ or $-NR^8R^9$ represents a saturated heterocyclic ring, it may suitably represent pyrrolidino, piperidino, morpholino or thiomorpholino. Where a saturated heterocyclic ring is formed by the group $-NR^8R^9$ and said ring is substituted by an oxo group, suitable heterocyclic groups include a 2-oxo-1-pyrrolidino, 4-oxo-3-thiazolidino or 2-oxo-tetrahydro-1,3-thiazine group.

A preferred group of compounds of general formula (I) is that wherein R^1 is attached at a position ortho to the group R^2 on the phenyl ring A in general formula (I).

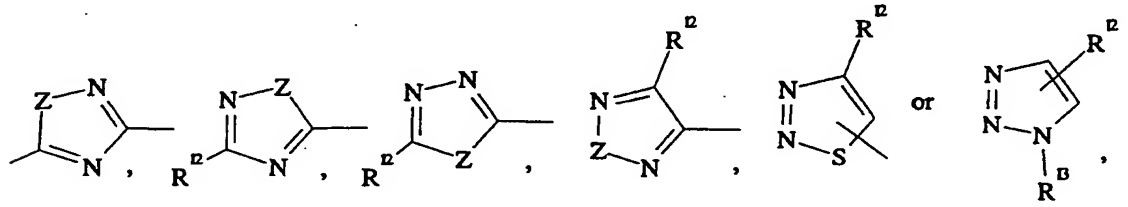
Suitably R^1 represents H, F, Cl, C_{1-3}alkyl such as methyl or C_{1-3}alkoxy such as methoxy. Preferably R^1 represents H or methyl.

The group R^2 will preferably be attached at the meta or, more preferably, the para position of the phenyl ring designated A in formula (I) above, relative to the amide linkage.

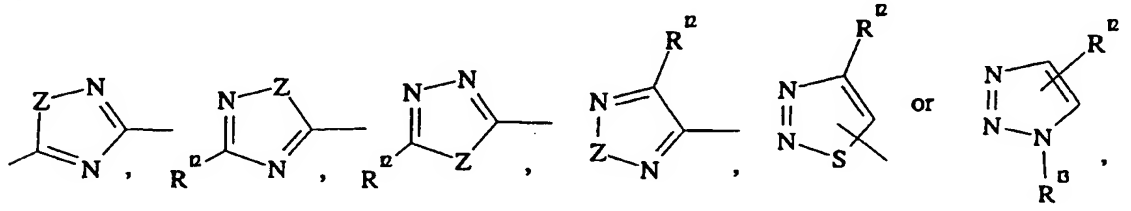
When R^2 represents an optionally substituted pyridyl group, it will preferably represent a 3-pyridyl or, more preferably, 4-pyridyl group, optionally substituted by one or two substituents as defined in formula (I).

A preferred group of compounds according to the intention is represented by compounds of formula (I) wherein R^2 is a pyridyl group optionally substituted by a single substituent, in particular a C_{1-6}alkyl, especially methyl, substituent. Preferably the single substituent will be ortho to the phenyl ring A in formula (I).

When R^2 represents a phenyl group substituted by a single substituent, the substituent will preferably be in the meta or, more preferably, the para position relative to the phenyl ring A in formula (I). When R^2 represents phenyl substituted by two substituents, one substituent is preferably ortho to the phenyl ring A. In particular, when R^2 represents phenyl substituted by a substituent of formula



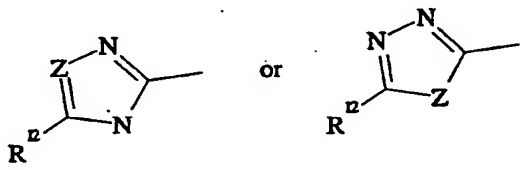
the substituent of formula



is preferably attached at the position para to the phenyl ring A in general formula (I). These compounds are particularly preferred.

Another preferred group of compounds of general formula (I) is that wherein R^2 phenyl is substituted by a heterocyclic substituent as above defined and is additionally substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy or C_{1-6}alkyl, which is (are) attached at a position ortho to the phenyl ring A in general formula (I).

A further preferred group of compounds of general formula (I) is that wherein R^2 represents a phenyl group substituted by the substituent



and optionally further substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy or C_{1-6}alkyl.

Another preferred group of compounds of general formula (I) is that wherein Z represents an oxygen atom.

Also preferred is the group of compounds of general formula (I) wherein R^4 is attached at the para-position relative to the amide linkage.

Suitably R^4 represents H, F, Cl, C_{1-6}alkyl such as methyl or, preferably, C_{1-6}alkoxy such as methoxy.

Suitably R^5 represents H, F or C_{1-6}alkoxy such as methoxy. Preferably R^5 represents H.

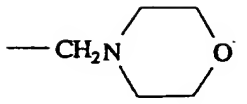
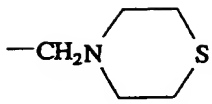
Preferably R^{11} represents C_{1-6}alkyl such as C_{1-3}alkyl, more preferably methyl.

Preferably R^{12} represents C_{1-6}alkyl, especially methyl, optionally substituted by C_{1-6}alkoxy, especially methoxy.

Preferably R^{13} represents C_{1-3}alkyl, especially methyl.

A further preferred group of compounds of general formula (I) is that wherein R^2 represents a phenyl group optionally substituted by one or two substituents selected from a halogen atom; or a C_{1-6}alkyl, especially methyl, group optionally substituted by a hydroxy group; or hydroxy; -CN; $-COR^6$ where R^6 is C_{1-6}alkyl especially methyl, ethyl, propyl or butyl; $-SR^6$ where R^6 is C_{1-6}alkyl especially methyl; $-SOR^6$ where R^6 is a C_{1-6}alkyl, especially methyl; $-CR^6=NOR^7$ where R^6 is H or C_{1-6}alkyl, especially methyl, and R^7 is H or C_{1-6}alkyl especially, methyl; $-CONR^6R^7$ where R^6 and R^7 each independently represent C_{1-6}alkyl, especially methyl, or $-NR^6R^7$ forms a saturated heterocyclic group which has six members and contains in the ring one oxygen atom, especially a morpholino ring; $-CONR^6(CH_2)_mOC_{1-4}$alkyl, where R^6 is C_{1-6}alkyl, especially methyl and m is two, especially the group $-CON(CH_3)(CH_2)_2OCH_3$; $-SO_2NR^6R^7$ where R^6 and R^7 each independently represent a H or C_{1-6}alkyl, especially methyl; $-OC(O)NR^6R^7$ where R^6 and R^7 each independently represent C_{1-6}alkyl, especially methyl; $-(CH_2)_nNR^8R^9$ where R^8 is H or C_{1-6}alkyl, especially methyl, R^9 is C_{1-6}alkyl, especially methyl, or $-COR^{12}$ (where R^{12} is C_{1-6}alkyl, especially methyl, C_{1-6}alkoxy, especially methoxy or ethoxy, or C_{1-4}alkoxyalkyl, especially methoxymethyl) or $-SO_2R^{13}$ (where R^{13} is C_{1-6}alkyl, especially methyl) or $-NR^8R^9$ forms a saturated heterocyclic group which has six ring members and contains in the ring one oxygen or sulphur atom, especially a morpholino, thiomorpholino or 2-oxo-1-pyrrolidino ring, and n is zero, 1 or 2; or a C_{1-4}alkoxyalkyl, especially methoxymethyl or methoxyethyl, substituted by C_{1-4}alkoxy, especially methoxy.

Another preferred group of compounds of general formula (I) is that wherein R^2 represents a phenyl group substituted by a group selected from hydroxymethyl, hydroxy, $-COCH_3$, $-SOCH_3$, $-C(CH_3)=NOH$, $-CON(CH_3)_2$, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2N(CH_3)_2$, $-OC(O)N(CH_3)_2$, $-NHCH_3$, $-N(CH_3)_2$, $-N(CH_3)COCH_3$, $-CH_2NHCO_2CH_2CH_3$, $-CH_2N(CH_3)COCH_2OCH_3$, $-NHSO_2CH_3$,

 ,  or $CH_2OCH_2CH_2OCH_3$.

and optionally further substituted by a chlorine atom or a methyl group.

Particularly preferred compounds of general formula (I) include:-

N-(4'-hydroxy[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide;

2-chloro-4'-[[4-methoxy-3-(4-methyl-1-piperazinyl)benzoyl]amino][1,1'-biphenyl]-4-carboxamide;

N-(4'-acetyl-2'-methyl-[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide;

4'-[[4-chloro-3-(4-methyl-1-piperazinyl)benzoyl]amino]-2-chloro-N,N-dimethyl[1,1'-biphenyl]-4-carboxamide;

4-methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl) phenyl]benzamide;

4-methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(3-pyridinyl) phenyl]benzamide;

2-methoxy-5-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl) phenyl]benzamide;
and their physiologically acceptable salts and solvates.

4-methoxy-N-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;

4-methoxy-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;

4-chloro-N-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;
and their physiologically acceptable salts and solvates.

5-Hydroxytryptamine (serotonin) is a neurotransmitter which is widely distributed within the central nervous system (CNS), platelets and the gastrointestinal tract. Changes in transmission in serotonergic pathways in the CNS are known to modify, for example, mood, psychomotor activity, appetite, memory and blood pressure. Release of 5-hydroxytryptamine from platelets can mediate vasospasm while changes in free 5-hydroxytryptamine levels in the gastrointestinal tract can modify secretion and motility.

Abundant pharmacological studies have led to the discovery of multiple types of receptors for 5-hydroxytryptamine, thus providing a molecular basis to the diversity of its actions. These receptors are classed as 5-HT_1, 5-HT_2 and 5-HT_3, with 5-HT_1 receptors being sub-classified as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D} and 5-HT_{1D}(like) receptors. The identification of these classes and sub-classes of receptor is based mainly on radiological binding studies.

Compounds having a selective antagonist action at 5-HT_{1D} receptors such as those described herein may exhibit a beneficial effect on subjects suffering from CNS disorders.

In the present specification, a 5-HT_{1D} antagonist is a non-naturally occurring (synthetic) compound that specifically and selectively antagonises 5-HT_{1D} receptors, i.e. - blocks the specific actions of 5-hydroxytryptamine mediated by the 5-HT_{1D} receptor. Such compounds may be identified by a high level of affinity (pKi $\geq$ 8) in the in vitro human cortex and guinea-pig striatum radioligand binding assays described by Hoyer et al, Neuroscience Letters, 1988, 85, p357-362. Activity at 5-HT_{1D} receptors may be confirmed in vivo using the guinea pig rotation model described by G A Higgins et al, Br. J. Pharmacol., 1991, 102, p305-310.

The affinity of a compound for 5-HT_{1A}, 5-HT_{1C} and/or 5-HT_2 receptors is measured using the in vitro tests described in the following publications:

5-HT_{1A} Gozlan et al, Nature, 1983, 305, p140-142

5-HT_{1C}	Pazos et al, Eur. J.Pharmacol., 1984, 106, p531-538
5-HT_2	Humphrey et al, Br. J. Pharmacol, 1988, 94, p1123-1132 (rabbit aorta model).

Thus, for example, compounds of the present invention have been shown to inhibit 5-hydroxytryptamine induced contraction of the dog isolated saphenous vein and to antagonise the 5-hydroxytryptamine induced inhibition of neurotransmission in central and peripheral neurones.

5-HT_{1D} antagonists, and in particular the compounds of the present invention, may therefore be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviour, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

5-HT_{1D} antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, according to a second aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

According to a further aspect of the present invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

According to another aspect of the invention, we provide the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned disorders.

According to a further aspect of the invention, we provide, a method of treating the aforementioned disorders which comprises administering to a patient in need of such treatment an effective amount of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In particular, according to another aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents,

for instance, different antidepressant agents such as tricyclic antidepressants (e.g. amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT reuptake inhibitors (e.g. fluvoxamine, sertraline, fluoxetine or paroxetine), and/or antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g. levodopa, preferably in combination with a peripheral decarboxylase inhibitor e.g. benserazide or carbidopa, or a dopamine agonist e.g. bromocriptine, lysuride or pergolide). It is to be understood that the present invention covers the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

Thus there is provided in a further or alternative aspect of the present invention a compound of general formula (I) or a physiologically acceptable salt or solvate

thereof and an antidepressant agent in the presence of each other in the human or non-human animal body for use in the treatment of the aforementioned disorders.

In a particular aspect of the present invention there is provided a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antiparkinsonian agent such as a dopaminergic antiparkinsonian agent, e.g. levodopa, and a peripheral decarboxylase inhibitor, e.g. benserazide or carbidopa, or a dopamine agonist e.g. bromocriptine, lysuride or pergolide in the presence of each other in the human or non-human animal body for use in the treatment of Parkinson's disease, dementia in parkinsonism, neuroleptic induced parkinsonism and tardive dyskinesias.

In using a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and one or more therapeutic agents it may be preferable to employ the active ingredients in the form of separate pharmaceutical formulations. A combined formulation can be used, however, in such a combined formulation the active ingredients must of course be stable and mutually compatible in the particular formulation employed.

It will be appreciated that administration of the active ingredients to a human or non-human patient may be simultaneous, separate or sequential. Where administration is not simultaneous, the delay in administering the second of the active ingredients should not be such as to lose the beneficial effect of the combination.

While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof. Such compositions may be presented for use

in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compositions according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxypropyl methylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation either orally or nasally the compositions according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compositions according to the invention may be prepared by mixing the various ingredients using conventional means.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the

discretion of the attendant physician or veterinarian. In general, however, a proposed dose of the compounds of the invention for administration in man is 0.5 to 1000mg, preferably I to 200mg of the active ingredient per unit dose which could be administered, for example, I to 4 times per day.

The compounds of the invention may be prepared by a number of processes as described in the following. In describing the processes which may be used for preparing the compounds of general formula (I) or intermediates useful in the preparation thereof, any of R^1-R^{18}, Z, and k in the various formulae are as defined in general formula (I) unless otherwise stated.

It will be appreciated that in the following methods for the preparation of compounds of general formula (I), for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where intermediates used to prepare compounds of general formula (I) contain amino functions. Standard protection and deprotection procedures can be employed, for example formation of a phthalimide (in the case of a primary amine), benzyl, trityl, benzyloxycarbonyl or trichloroethoxycarbonyl derivatives. Subsequent removal of the protecting group is achieved by conventional procedures. Thus a phthalimide group may be removed by treatment with hydrazine or a primary amine, for example methylamine. Benzyl or benzyloxycarbonyl groups may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium, and trichloroethoxycarbonyl derivatives may be removed by treatment with zinc dust. Trityl groups may be removed under acidic conditions using standard procedures.

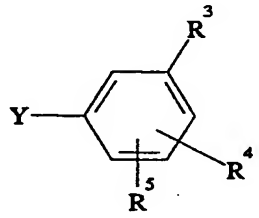
Conventional protecting groups are described in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wutts, John Wiley & Sons, 1991.

It may also be necessary in some cases to protect carboxylic acid groups (e.g. as esters) or aldehyde or ketone groups (e.g. as acyclic or cyclic acetals or ketals or as thioacetals or thioketals). Subsequent removal of these protecting groups is achieved by conventional procedures. Thus for example alkyl esters may be

removed under conditions of acidic or basic hydrolysis, benzyl esters may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium. Acyclic or cyclic acetals or ketals may be removed under conditions of acidic hydrolysis and thioacetals and thioketals may be removed using a mercuric salt.

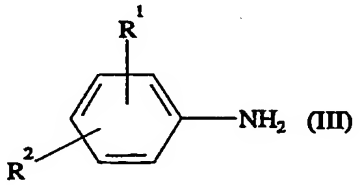
Hydroxyl groups may also need protection and these may be adequately protected under amenable conditions as their esters or trialkylsilyl, tetrahydropyran and benzyl ethers. Such derivatives may be deprotected by standard procedures.

According to one general process (1), the compounds of general formula (I) may be prepared by a carbonylation reaction involving a compound of formula (II)



(II)

(where Y represents a halogen atom e.g. bromine or iodine or the group $-OSO_2CF_3$) and an aniline compound (III)

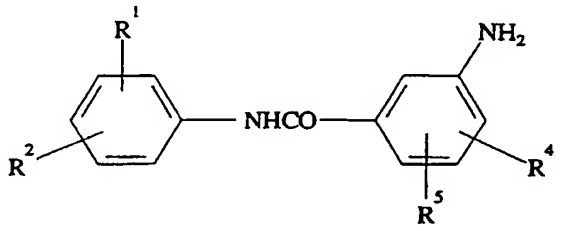


(III)

The reaction takes place, for example, in the presence of carbon monoxide using a palladium salt as a catalyst. The reaction is effected in the presence of a suitable base e.g. a trialkylamine such as triethylamine or tri-n-butylamine and may be conducted in a suitable solvent such as an amide e.g. dimethylformamide or a nitrile eg acetonitrile at a temperature within the range of -10^0C to $+120^0C$.

Suitable palladium salts for the reaction include triarylphosphine palladium (II) salts such as bis(triphenylphosphine)palladium (II) chloride.

According to another general process (2), the compounds of general formula (I) may be prepared by treating a compound of formula (IV)



(IV)

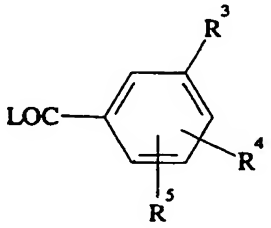
with an amine dihalide of formula (V)

$$R^{11}N(CH_2CH_2Hal)_2 \qquad (V)$$

(where Hal is a chlorine, bromine or iodine atom).

The reaction may conveniently take place in the presence of a polar solvent such as an alcohol (e.g. n-butanol) or a nitrile (e.g acetonitrile), optionally in the presence of a base, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, or alternatively in a non-polar solvent (e.g. chlorobenzene) in the absence of a base. The reactions may conveniently be carried out at an elevated temperature, for example, reflux.

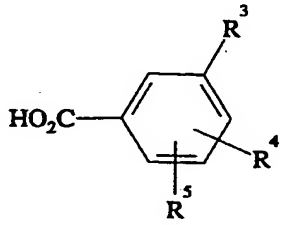
According to another general process (3), the compounds of general formula (I) may be prepared by reacting an aniline of formula (III) with an activated carboxylic acid derivative of formula (VI)



(VI)

(where L is a leaving group).

Suitable activated carboxylic acid derivatives represented in formula (VI) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides. These activated derivatives may be formed from the corresponding acid of formula (VII)



(VII)

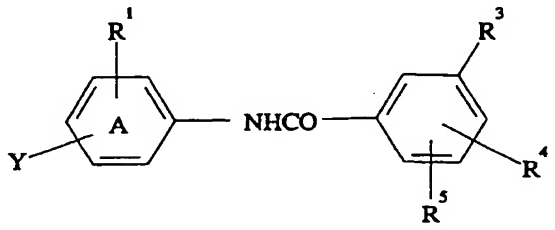
by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g. trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

Activated carboxylic acid derivatives of formula (VI) may also be prepared in situ by the reaction of the corresponding acids of formula (VII), with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

The conditions under which the activated carboxylic acid derivatives of formula (VI) are formed and subsequently reacted with the anilines of formula (III) will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (III) and (VI) may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halohydrocarbon such as dichloromethane at a temperature within the range -25^{0}C to +120^{0}C. The reaction may optionally be carried out in the presence of a base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C, for example, room temperature.

According to another general process (4a), the compounds of general formula (I) may be prepared by treating a compound of formula (VIIIa)



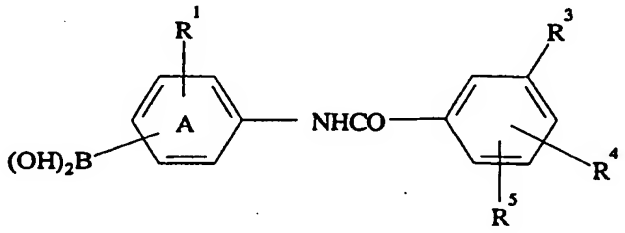
(VIIIa)

(where Y represents a bromine or iodine atom or the group $-OSO_2CF_3$) with a compound of formula (IXa)

$$R^2B(OH)_2 \qquad \text{(IXa)}$$

or an ester, an anhydride or a salt (e.g. lithium) thereof.

Alternatively, according to the general process (4b), the compounds of general formula (I) may be prepared by treating a compound of formula (VIIIb)



(VIIIb)

or an ester, an anhydride or a salt (e.g. lithium) thereof, with a compound of formula (IXb)

$$R^2\text{-}Y \qquad \text{(IXb)}$$

where Y represents a bromine or iodine atom or the group $-OSO_2CF_3$.

Both reactions may be effected in the presence of a transition metal catalyst such as $(Ph_3P)_4Pd$ (where Ph represents phenyl) in a suitable solvent such as an ether (eg 1,2-dimethoxyethane or tetrahydrofuran) in the presence or absence of water, or an aromatic hydrocarbon (eg benzene). The reaction is preferably carried out in the presence of a base such as an alkali or alkaline earth metal carbonate (eg sodium carbonate) at a suitable temperature up to reflux.

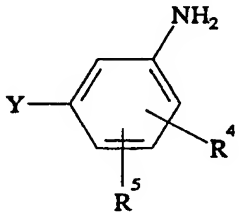
Compounds of general formula (I) may also be prepared from different compounds of formula (I) by standard methods of interconversion. For instance, when R^2 contains a hydroxy or alkoxy group and/or when R^4 and/or R^5 represents hydroxy or alkoxy these groups may be interchanged by standard methods of O-alkylation or O-dealkylation. Thus, for example, a compound in which R^4 represents hydroxy may be prepared by treating a corresponding compound in which R^4 represents methoxy with a reagent system capable of removing the methyl group e.g. a mercaptide such as sodium ethylmercaptide in a solvent such as dimethylformamide, lithium iodide in collidine, boron tribromide in a halohydrocarbon solvent e.g. methylene chloride or molten pyridine hydrochloride.

When R^2 contains a hydroxymethyl group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 contains a group COR^6 (where R^6 is a hydrogen atom) or CO_2H. Thus, for example, oxidation may be effected using a suitable oxidising agent such as a manganese oxidising agent (eg manganese dioxide) in a solvent such as an ether (eg 1,4-dioxan) at a suitable temperature up to reflux, a chromium oxidising agent (eg Jones reagent) or pyridinium dichromate in a suitable solvent such as a halohydrocarbon (e.g. methylene chloride).

When R^2 contains an aldehyde group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 contains a group CO_2H. Thus, for example, oxidation may be effected using a suitable oxidising

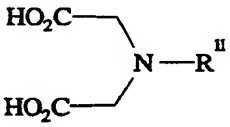
agent such as a source of silver (I) ions (e.g. silver nitrate) in aqueous alkali optionally in the presence of a cosolvent such as an alcohol (e.g. methanol).

Intermediates of formula (II) may be prepared from the corresponding compound of formula (X)



(X)

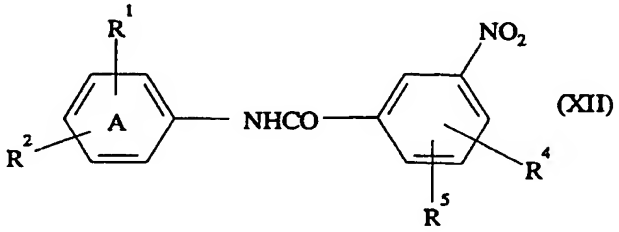
by reaction with a compound of formula (XI)



(XI)

in the presence of acetic anhydride, followed by reduction of the diketopiperazine intermediate thus formed using, for example, borane. The reaction may be carried out at a temperature between 50°C and reflux, and optionally in a solvent such as an ether, e.g. tetrahydrofuran, or toluene.

Intermediates of formula (IV) may be prepared by reduction of the corresponding nitro compound of general formula (XII)



(XII)

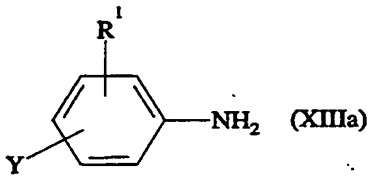
The reduction may be effected by catalytic hydrogenation using a metal catalyst such as palladium or platinum or oxides thereof, preferably, in a solvent such as

an alcohol e.g ethanol, or alternatively by using Raney nickel and hydrazine in a solvent such as an alcohol e.g. ethanol, or alterntively by using titanium trichloride in a suitable solvent such as aqueous acetone.

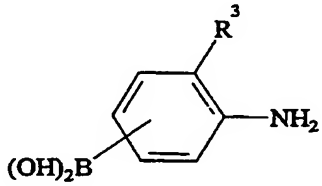
Intermediates of formula (XII) may be prepared by condensing a compound of formula (VI) wherein R^3 represents a nitro group with a compound of formula (III) under the conditions of general process (3).

It will be appreciated that, where necessary, a halogen substituent may be converted into a carboxyl group using standard methodology thus, for example, intermediates of formula (VII) may be prepared from an intermediate of formula (II) by lithiation using, for example, n-butyl lithium followed by quenching with carbon dioxide.

Intermediates of formula (VIIIa) and (VIIIb) may be prepared by reaction of a compound of formula (VI) with a compound of formula (XIIIa) or (XIIIb), respectively,



(XIIIa)



(XIIIb)

according to the method of general process (3).

The boronic acid intermediates of formulae (VIIIb), (IXa) and (XIIIb) or their esters, anhydrides or salts may be used in situ under the conditions described above for general process (4).

Intermediates of formula (III) may be prepared by the reaction of a compound of formula (IXa) or (IXb) with a compound corresponding formula (XIIIa) or (XIIIb) according to the method of general process (4).

Intermediates of formula (III) may also be prepared from the corresponding carboxylic acid using conventional procedures (e.g. by Curtius rearrangement).

Intermediates of formulae, (V), (X), (XI), (XIIIa) and (XIIIb) are either known compounds or may be prepared by standard methodology or methods analogous to those described herein.

Intermediates containing the group R^2 may be prepared by methods described herein and using techniques well known in the art, such as those described in "Comprehensive Organic Chemistry", Vol. 4 by D. Barton and W.D. Ollis, Pergamon Press, Oxford (1979) (see especially pages 1020-1050 for five-membered mixed heteroatom ring systems) or in "Comprehensive Heterocyclic Chemistry", Vol. 6 by A R Katritzky and C W Rees, Pergamon Press, Oxford (1984) (see pages 365-577).

Acid addition salts of the compounds of general formula (I) may be prepared by treating the corresponding free base with a suitable acid using conventional methods. Thus, for example, a generally convenient method of forming the acid addition salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent eg an alcohol such as ethanol or an ester such as ethyl acetate.

Salts of compounds of general formula (I) may also be converted to different physiologically acceptable salts of compounds of general formula (I) using conventional methods.

The invention is illustrated but not limited by the following examples in which temperatures are in ^0C. Thin layer chromatography (T.l.c.) was carried out on silica plates.

The following abbreviations are used :-
DMF - dimethylformamide; TEA - triethylamine; HMPA - hexamethylphosphoramide; THF - tetrahydrofuran; MSC - methanesulphonyl chloride; BTPC - bis(triphenylphosphine)palladium (II) chloride; DME - 1,2-

dimethoxyethane; DMA - dimethylamine; DMSO - dimethylsulphoxide; SPC - Short path chromatography carried out on silica (Merck 7747) unless otherwise stated. FCC - Flash column chromatography carried out on silica (Merck 9385). 'Dried' refers to drying using sodium sulphate or magnesium sulphate unless otherwise stated.

The following solvent systems were used:-
System A - dichloromethane:ethanol:0.88 ammonia; System B - dichloromethane:methanol:0.88 ammonia.

Intermediate 1
[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl]boronic acid bimolecular anhydride

n-Butyl lithium (1.6M; 9.7ml) was added, over 8 min, under nitrogen to a stirred, cooled (-70^0) solution of 1-bromo-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzene (4g) in dry THF (40ml). After a further 25 min, the resulting solution was added over 10 min to a stirred cooled (-66^0) solution of tri-isopropyl borate (10ml) in THF (40ml) and the mixture stirred at room temperature for 2h. Water (10ml) and, after a further 5 min, pH 6.5 phosphate buffer (100ml) and ether (50ml) were added and the mixture stirred vigorously for 10 min. The aqueous layer was extracted with ether (2x70ml) and the combined organic solutions dried and evaporated in vacuo to leave a white solid. Crystallisation from ether gave the title compound (2.02g) as a white solid.
T.l.c. dichloromethane-methanol (96:4) Rf 0.56

Intermediate 2
Methyl 4-methoxy-3-(4-methyl-1-piperazinyl)benzoate hydrochloride

A suspension of 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (1.92g) and methyl 3-amino-4-methoxybenzoate (1.81g) in n-butanol was refluxed with stirring for 19h. Anhydrous sodium carbonate (0.54g) was added and refluxing continued for 8.5h. The solvent was then removed to give an oil which was taken up in water (50ml) and 2N hydrochloric acid (50ml) and extracted with ethyl acetate (2x50ml). The acid solution was then basified with sodium

bicarbonate and re-extracted with ethyl acetate (3x50ml). The extracts were dried and concentrated to a semi-solid (2.47g) which was absorbed from System A (200:8:1) (5ml) onto Kieselgel G (100g). Elution with the same solvent gave starting material and minor basic impurities. Further elution with System A (100:8:1) (450ml) gave first minor impurities and later fractions afforded the free base of the desired product as a gum (0.48g). This was taken up in methanol (5ml), filtered and treated with ethereal hydrogen chloride and diluted to 25ml with ethyl acetate. A cream coloured solid separated and was collected giving the title compound (0.586g), m.p. 190-194^0. Recrystallisation from methanol-ethyl acetate afforded a sample for analysis.

Analysis Found:	C,55.7; H,7.2; N,9.2; Cl,12.0
$C_{14}H_{20}N_2O_3$.HCl requires	C,55.9; H,7.0; N,9.3; Cl,11.8%

Intermediate 2 was also made by the alternative two-step reaction as follows:

(a) Methyl 3-(2,6-dioxo-4-methyl-1-piperazinyl)-4-methoxybenzoate

N-(Carboxymethyl)-N-methylglycine (812mg) was suspended in acetic anhydride (4ml) and heated to reflux for 30min. The excess acetic anhydride was then evaporated off and the dark residue treated with a solution of methyl 3-amino-4-methoxybenzoate (1g) in toluene (20ml). The mixture was stirred at 20^o for 5 min, then at 100^o for 10min. The toluene was evaporated off giving a fawn crystalline solid which was suspended in acetic anhydride (5ml) and heated to reflux for 10min. The excess acetic anhydride was evaporated off giving a brown solid which was crystallised from methanol (2ml) giving the title compound as colourless microneedles (665mg) m.p. 157-8^o.

(b) Methyl 4-methoxy-3-(4-methyl-1-piperazinyl)benzoate

To a stirred solution of the product of step (a) (400mg) in dry THF (15ml) at reflux, under nitrogen, was added dropwise borane:THF complex (1M solution, 5.5ml). Heating was maintained for 18h whereupon the mixture was allowed to cool, and hydrochloric acid (2N,2ml) was added, dropwise at first. The mixture was then heated to reflux for 1.5h and the solvents evaporated. The residue was partitioned between 8% sodium bicarbonate solution (30ml) and ethyl acetate (2x35ml). Evaporation of the dried extracts gave a yellow oil which was purified by

FCC eluting with System A (200:8:1) to give the title compound (Intermediate 2) as a pale yellow oil (176mg).
T.l.c. System A (100:8:1) Rf 0.58

Intermediate 3
4-Bromo-N,N,3-trimethylbenzamide
A mixture of 4-bromo-3-methylbenzoic acid (1.0g) and thionyl chloride (3ml) was refluxed under nitrogen for 1h and evaporated. The residue in THF (10ml) was treated with aqueous dimethylamine (40%; 3ml) in one portion. The solution was left to cool to room temperature (15min) and was treated with aqueous sodium carbonate (1M; 50ml) and extracted with ethyl acetate (2 x 100ml). The dried extract was evaporated to give the title compound as a colourless oil (0.95g).
T.l.c. ether Rf 0.4

Intermediate 4
3-Chloro-4-hydroxy-N,N-dimethylbenzamide
A suspension of 3-chloro-4-hydroxybenzoic acid hemihydrate (3.0g) in thionyl chloride (10ml) was refluxed under nitrogen for 2h. Tetrahydrofuran (10ml) was added to aid solubility and the suspension was refluxed for 3h and evaporated. The residue was suspended in THF (20ml) and was treated in 3 portions with aqueous dimethylamine (40%; 15ml). The solution was stirred for 1h, treated with aqueous sodium bicarbonate (1N; 50ml) and extracted with dichloromethane-methanol (19:1; 3x100ml). The dried extract was evaporated and the residue was crystallized from ethyl acetate (30ml) to give the title compound as a white solid (1.0g).
T.l.c. ether Rf 0.3.

Intermediate 5
2-Chloro-4-[(dimethylamino)carbonyl]phenyl trifluoromethanesulphonate
Trifluoromethanesulphonic anhydride (315mg) was added dropwise to a solution of Intermediate 4 (250mg) and pyridine (0.2ml) in dichloromethane (5ml) at 0°C under nitrogen. The solution was stirred at room temperature for 1h and added to hydrochloric acid (1N;25ml). The mixture was extracted with dichloromethane (25ml) and the dried extract was evaporated. The residue was purified on a

column of silica (Merck 9385) eluted with ether to give the title compound as a colourless oil (333mg).
T.1.c. ether Rf. 0.5.

Intermediate 6

N-(4-Bromophenyl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide

A solution of the free base of Intermediate 2 (1g) and sodium hydroxide (0.4g) in aqueous methanol (1:1, 60ml) was heated at reflux for 3.5h. The clear colourless solution was concentrated, acidified with 2N hydrochloric acid and concentrated to dryness. The residual white solid was then suspended in dry pyridine (15ml) and the mixture chilled in an ice-salt bath and treated with thionyl chloride (242µl) with stirring. The mixture was stirred in the ice-salt bath for 1h, then 4-bromobenzenamine (573mg) was added and the mixture allowed to reach room temperature. Stirring was continued for 18h, then the solution was diluted with water (75ml), followed by sodium carbonate (2N;75ml). The aqueous solution was extracted with ethyl acetate (3x150ml). The combined organic extracts were washed with brine (150ml) and water (150ml), dried, filtered and evaporated in vacuo to give an oily residue. Purification by SPC eluting with System A (98:2:0.2) gave the title compound as a cream coloured foam (455mg), m.p. 72-73°C.

Analysis Found: C,55.9; H,5.7; N,10.2; Br,18.55;
$C_{19}H_{22}BrN_3O_2$. 0.45 C_2H_6O requires C,56.2; H,5.9; N,9.9; Br, 18.8%

Intermediate 7

[4-[[4-Methoxy-3-(4-methyl-1-piperazinyl)benzoyl]amino]phenyl] boronic acid

A stirred solution of Intermediate 6 (1.7g) in dry THF (100ml), under nitrogen, at -78°C was treated dropwise with n-butyllithium (7.9ml of a 1.59M solution in hexane). After 1h, triisopropylborate (2.9ml) was added dropwise at -78°C and the reaction was stirred at this temperature for 2h. Hydrochloric acid (2N, 2.6ml) was added followed by water (25ml) and the resultant mixture was evaporated to yield a yellow residue, which was preadsorbed onto silica [Merck Art. 7734]. Purification by FCC eluting with System A (65:35:3.5) gave the title compound as a yellow-foam (1.403g) m.p. 104-106°C (decomp).

Intermediate 8

(4-Formyl-2-methylphenyl)boronic acid

A stirred solution of 2,5-dibromotoluene (5.00g) in dry THF (200ml) under nitrogen at -78° was treated dropwise with n-butyllithium (11.8ml, 1.69M in hexane). After 1h, DMF (1.6ml) was added and the mixture was allowed to warm to 0° and then recooled to -78° and treated with more n-butyllithium (11.8ml, 1.69M in hexane). After 1h, triisopropyl borate (7.0ml) was added and the cooling bath removed. After 1h, 2N hydrochloric acid (80ml) was added and the THF removed under vacuum. The residue was extracted with ether (3 x 100ml) and the combined extracts were dried and evaporated to give an oil. SPC (Merck 7729) eluting with chloroform-ethanol (50:1) gave the product (2.21g) as an almost colourless oil. Addition of acetone (50ml) and evaporation to dryness gave the title compound (1.31g) as a colourless solid.

T.l.c. chloroform:ethanol (50:1) Rf 0.25

Intermediate 9

Methyl 4-chloro-3-(4-methyl-1-piperazinyl)benzoate

A suspension of methyl 3-amino-4-chlorobenzoate (3.72g) in chlorobenzene (20ml) was treated with 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (3.90g). The resulting mixture was heated to reflux (150-180°C) under nitrogen for 16 hours before cooling, diluting with dichloromethane, and extracting with water (15ml). 2N hydrochloric acid (2x50ml) was added to the second extraction to ensure complete formation and extraction of salt. The aqueous layers were washed with dichloromethane (3x40ml). The combined, dried extracts were concentrated in vacuo and the residue purified by FCC eluting with System A (300:8:1) to give a yellow oil which crystallised upon cooling. The crystalline solid was dried in vacuo to give the title compound as a pale yellow crystalline solid (1.77g). m.p. 78-79°C.

Intermediate 10

N-(4-Bromophenyl)-4-chloro-3-(4-methyl-1-piperazinyl)benzamide

A suspension of sodium hydride (250mg, 60% dispersion in oil) in DMSO (3ml) was treated with 4-bromobenzenamine (1.09g). After 10 min the mixture was treated with Intermediate 9 (1.69g). The mixture was stirred at room temperature for 60 hours, poured into water (50ml) and stirred for a further 1 hour. The

precipitate was filtered off, the residue washed well with water and then triturated in dry ether to give a solid (2.50g). The solid was dissolved in a mixture of water (50ml) and dichloromethane (50ml). The organic layer was separated, dried, concentrated in vacuo and the residue triturated in ether to give the title compound as a white solid (1.47g) m.p. 182-183°C.

Intermediate 11

[4-[[4-Chloro-3-(4-methyl-1-piperazinyl)benzoyl]amino]phenyl]boronic acid

A solution of Intermediate 10 (680mg) in dry THF (15ml) was cooled to -74°C and treated dropwise with n-butyl lithium (1.56mmole in hexane, 2.15ml), the temperature being maintained between -70 and -74°C during addition. The mixture was stirred at -74°C for 30 min before treating dropwise with triisopropylborate (0.78ml). The reaction was stirred at -74°C for 30 mins before warming to room temperature and stirring for 3 hours. The mixture was concentrated in vacuo, the residue mixed with water (50ml) and neutralised with 2N hydrochloric acid. The mixture was then extracted with ethyl acetate (3x75ml), and the combined extracts dried and concentrated in vacuo to give a glass which when triturated with ether gave the title compound as a cream-coloured solid (485mg).

n.m.r. (DMSO + D_2O) δ 2.28 (3H,s), 2.56 (4H,br.m) 3.09 (4H,m), 7.54-7.70 (3H,m), 7.70-7.84 (4H,m).

Intermediate 12

3,4-Dimethoxy-5-nitrobenzoic acid

To a solution of potassium permanganate (3.05g) in water (100ml) was added to a solution of 3,4-dimethoxy-5-nitrobenzaldehyde (2.7g) in acetone (80ml). The mixture was then stirred at 20° for 18h whereupon the acetone was evaporated and the residue acidified (2N HCl) and was then decolourised by the addition of sodium metabisulphite solution. The mixture was then extracted with ethyl acetate (3x200ml) and the dried extracts evaporated to give the title compound as a colourless solid (2.08g) m.p. 197-198°.

Intermediate 13

Methyl 3,4-dimethoxy-5-nitrobenzoate

Intermediate 12 (1g) was dissolved in methanol:conc. sulphuric acid (9:1; 20ml) and was stirred at 20° for 2h, and was then heated to reflux for 2h. The cooled mixture was added to 8% $NaHCO_3$ solution (50ml). The methanol was then evaporated and the residue extracted with ethyl acetate (2x75ml). The dried extracts were evaporated to give the title compound as a cream solid (1g), m.p. 75-76°.

Intermediate 14

Methyl 3-amino-4,5-dimethoxybenzoate

A solution of Intermediate 13 (990mg) in ethanol (15ml) was hydrogenated over 10% palladium on carbon for about 5h. The mixture was filtered and was evaporated to give a pale pink oil which crystallised to give the title compound (883mg).

T.1.c ethyl acetate:hexane (1:2) Rf 0.15.

Intermediate 15

2-Methoxy-3-(4-methyl-1-piperazinyl)benzoic acid

1-(2-Methoxyphenyl)-4-methylpiperazine (10.0g) was added in ether (20ml) dropwise to a solution of n-butyllithium in hexane (1.6M; 36ml) and N,N-tetramethylethylenediamine (5.6g) under nitrogen at room temperature. The resulting suspension was stirred for 6h and was added slowly to a mixture of solid carbon dioxide (50g) and THF (50ml). The mixture was allowed to warm to room temperature and was treated with water (150ml). The aqueous solution was washed with ether (2x200ml), acidified with hydrochloric acid (2N) and evaporated. The solid was treated with methanol (150ml), filtered and the filtrate was evaporated to give the title compound as a white solid (15.0g)

n.m.r. (D_2O) δ 3.04 and 3.0-3.15 (7H, m + s), 3.38 (2H, br.m), 3.65 (2H, br.d), 3.9 (3H, s), 7.15-7.35 (3H, m).

Intermediate 16

Butyl 3,4-dimethoxy-5-(4-methyl-1-piperazinyl)benzoate

A mixture of Intermediate 14 (868mg), sodium carbonate (1.74g), 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (791mg) in n-butanol (35ml) was heated at reflux for 48h. The mixture was allowed to cool and the solvent

evaporated. Water (40ml) was added and the mixture extracted with ethyl acetate (2x50ml). The dried extracts were evaporated to give a red oil (1.55g) which was chromatographed on silica gel eluting with System A (200:8:1) to give the title compound as a red oil (276mg).
T.l.c. System A (200:8:1) Rf 0.24.

Similarly prepared were:-

Intermediate 17
Butyl 2-methoxy-5-(4-methyl-1-piperazinyl)benzoate as a brown oil (1.12g).
T.l.c. System A (200:8:1), Rf 0.43.
From methyl 5-amino-2-methoxybenzoate (2.19g) and 2-chloro-N-(2-chloroethyl)-N-methylethanamine hydrochloride (2.33g).

Intermediate 18
Butyl 2-hydroxy-5-(4-methyl-1-piperazinyl)benzoate, hydrochloride as a white solid (230mg).
T.l.c. System A (200:8:1), Rf 0.26.
From methyl 5-amino-2-hydroxybenzoate (2.0g) and 2-chloro-N-(2- chloroethyl)-N-methylethanamine hydrochloride (2.3g). The free base of the title compound was dissolved in methanol and ethereal hydrogen chloride added. The title compound was collected by filtration as a white precipitate.

Intermediate 19
3-(4-Bromo-3-methylphenyl)-5-methyl-1,2,4-oxadiazole
A solution of sodium methoxide (1.93g) in methanol (15ml) was added dropwise over 10 min to a solution of hydroxylamine hydrochloride (2.48g) in methanol (30ml). The mixture was stirred for 1h at 20° and was then filtered. 4-Bromo-3-methylbenzonitrile (7g) was then added to the filtrate, and the mixture heated to reflux for 18h. The solvent was then evaporated giving a grey solid, a portion of which (2.2g) was dissolved in acetic anhydride (6ml) and heated to 80° for 18h. The reaction was cooled and was poured into water (100ml). The solid was separated, collected and recrystallised from isopropanol (20ml) giving the title compound as colourless microcrystals (896mg) m.p. 78°.

Intermediate 20

Methyl 4-bromo-3-methylbenzoate

4-Bromo-3-methylbenzoic acid (10g) was suspended in methanol (50ml) containing conc. sulphuric acid (2ml). The mixture was heated to reflux for 18h. On addition of 8% $NaHCO_3$ (100ml) to the cooled reaction, a solid was formed which was collected by filtration. Drying in vacuo at 40-45° gave the title compound as a liquid which recrystallised on cooling (10.25g) m.p. 39.5-40.5°C

Intermediate 21

4-Bromo-3-methylbenzoic acid hydrazide

A solution of Intermediate 20 (2g) in methanol (20ml) containing hydrazine hydrate (1.1ml) was heated to reflux for 18h. On cooling a solid crystallised which was collected by filtration and washed with ether to give the title compound as colourless needles (1.81g), m.p. 164-166°C.

Intermediate 22

2-(4-Bromo-3-methylphenyl)-5-methyl-1,3,4-oxadiazole

Intermediate 21 (1g) in 1,1,1-triethoxyethane (10ml) was heated to reflux for 18h. The mixture was then allowed to cool and the title compound collected by filtration as a colourless powder (816mg) m.p. 135-137°C.

Example 1

N-(4'-Hydroxy[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide

A stirred mixture of Intermediate 6 (200mg), Intermediate 1 (151mg), tetrakis(triphenylphosphine)palladium (0) (35mg) and anhydrous sodium carbonate (64mg) in water (4ml) and DME (4ml) under nitrogen, was heated at reflux for 24hours. The reaction mixture was then cooled to room temperature and the reaction contents adsorbed onto silica gel (3g). Purification by SPC eluting with System A (95:5:0.5) afforded an impure sample which was further purified by SPC eluting with System A (97:3:0.3) to give the title compound (141mg) as a white foam. m.p. 135-136°C.

Analysis found:	C,70.6; H,6.6; N,9.4;
$C_{25}H_{27}N_3O_3.0.6C_2H_5OH$ requires:	C,70.7; H,6.9; N,9.4%

Similarly prepared was:-

Example 2

N-(4'-Formyl-2'-methyl-[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide as a white foam-like solid (398mg) m.p. 85-86°C

Analysis Found: C,70.7; H,6.3; N,8.9

$C_{27}H_{29}N_3O_3.0.42\ H_2O.0.5\ CH_3CO_2C_2H_5$ requires C,70.3; H,6.9; N,8.5%

Water Analysis Found: 1.65% w/w $H_2O \equiv 0.42$ mol H_2O

From Intermediate 6 (450mg) and Intermediate 8 (200mg). Purification by SPC eluting with System A (97:3:0.3) afforded the title compound.

Example 3

N-(4'-Cyano-2'-methyl-[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide

A mixture of 4-bromo-3-methylbenzonitrile (150mg), Intermediate 7 (282mg), sodium carbonate (267mg) and tetrakis(triphenylphosphine) palladium (0) (17mg) in 1:1 aqueous DME (20ml) was heated to reflux for 18h. The mixture was evaporated onto silica gel and purified by chromatography eluting with System A (200:8:1) to give the title compound as colourless foam (126mg)

T.l.c. System A (100:8:1) Rf 0.40

Assay Found: - C, 71.25; H, 6.3; N, 11.95;

$C_{27}H_{28}N_4O_2.\ 0.75H_2O$ requires: - C, 71.4; H 6.55; N, 12.35%

Example 4

4-[[4-Methoxy-3-(4-methyl-1-piperazinyl)benzoyl]amino]-N,N,2,-trimethyl-[1,1'-biphenyl]-4-carboxamide

A solution of Intermediate 3 (204mg) and Intermediate 7 (302mg) in DME (10ml) and 2N sodium carbonate (3ml) under nitrogen was treated with tetrakis(triphenylphosphine)palladium (0) (40mg) and then heated to reflux for 20 hours. The reaction mixture was then cooled to room temperature, added to water (50ml) and extracted with dichloromethane (3x40ml). The combined, dried extracts were concentrated in vacuo to give a pale yellow solid which was purified by FCC eluting with System A (200:8:1) to give a cream solid. The solid was was

triturated in ether and dried in vacuo to give the title compound as a cream-coloured solid (232mg).
m.p. 256-257.5°C
T.l.c. System A (75:8:1) Rf = 0.45.

Similarly prepared were:-

Example 5
2-Chloro-4'-[[4-methoxy-3-(4-methyl-1-piperazinyl)benzoyl]amino] [1,1'-biphenyl]-4-carboxamide as a white solid (45mg) m.p. 230-232°C
T.l.c. System B (90:10:1) Rf 0.6.
From a mixture of Intermediate 7 (250mg), Intermediate 5 (200mg), aqueous sodium carbonate (0.5ml; 2N), tetrakis(triphenylphosphine)palladium (0) and DME (5ml).

Example 6
N-(4'-Acetyl-2'-methyl-[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide as a white solid (137mg). m.p. 104-107°C.
T.l.c. System B (90:10:1) Rf 0.6
From a mixture of Intermediate 7 (250mg), 1-(4-bromo-3-methylphenyl)ethanone (115mg), aqueous sodium carbonate (2N,2ml), DME (8ml) and tetrakis(triphenylphosphine)palladium (0) (20mg).

Example 7
4'-[[4-Chloro-3-(4-methyl-1-piperazinyl)benzoyl]amino]-2-chloro-N,N-dimethyl[1,1'-biphenyl]-4-carboxamide as a cream-coloured powder (32mg). m.p. 247-248.5°C
Assay found: C,59.7; H,5.2; N,10.2;
$C_{27}H_{28}Cl_2N_4O_2$ requires: C,59.6; H,5.2; N,10.3%
From a mixture of Intermediate 11 (150mg) and Intermediate 5 (165mg) in DME (4ml) and water (1ml) containing anhydrous sodium carbonate (53mg) treated under nitrogen with tetrakis(triphenylphosphine)palladium (0) (20mg).

Example 8

4-Methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl]benzamide, dihydrochloride

A solution of Intermediate 2 (0.337g) and sodium hydroxide (0.13g) in aqueous methanol (1:1, 20ml) was refluxed for 2.75h. The clear solution was concentrated, acidified with 2N hydrochloric acid and concentrated to dryness. The residual off-white solid was then suspended in dry pyridine (5ml) and the mixture chilled in an ice salt bath and treated with thionyl chloride (0.147g) with stirring. The mixture was stirred in the ice-salt bath for 1h, then 4-(4-aminophenyl)pyridine (0.17g) was added and the mixture allowed to warm to room temperature. After about 30 mins, a pale yellow solid separated. Stirring was continued for 5.5h, then the solution was diluted with water (25ml) and treated with 2N sodium carbonate (25ml). The precipitated solid was extracted with ethyl acetate (3x100ml) and the extracts washed with brine (3x25ml) and water (2x25ml) and dried. Removal of the solvent gave a solid (0.37g) which was taken up in System A (10ml, 100:8:1) and absorbed onto Kieselgel 60 (50g). Elution with the same solvent (275ml) returned starting amine. Further elution with this solvent (350ml) afforded the product (0.27g) which crystallised on trituration with a little ether. This material was taken up in methanol (6ml), the solution filtered, treated with ethereal hydrogen chloride until a white precipitate formed and then diluted to 25ml with ethyl acetate. The solid was collected and washed well with ethyl acetate to give the title compound as a solid (0.365g) m.p. 282^0 (dec) (softens and shrinks at 279^0). Recrystallisation from methanol:ethyl acetate gave an analytical sample m.p. 282^0 (dec).

T.l.c. System A (100:8:1), Rf 0.6

Example 9

4-Methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(3-pyridinyl)phenyl] benzamide

A stirred mixture of Intermediate 7 (0.3g), 3-bromopyridine (78µl), tetrakis(triphenylphosphine)palladium (0) (0.047g) and sodium carbonate (0.26g) in DME (6ml) and water (6ml) was heated at reflux under nitrogen for 8h. The reaction mixture was then adsorbed onto silica gel (Merck 7734) and the silica applied as a plug to a short path column of silica gel (Merck 7729). Elution with System A (95:5:0.5) gave the title compound as a white solid (0.253g) m.p. 138-140°C.

Analysis Found C,70.2; H,6.7; N,13.6

$C_{24}H_{26}N_4O_2.0.48H_2O.0.05CH_3CO_2C_2H_5$

requires C,69.95; H,6.6; N,13.5%

Water Assay Found: 2.05% w/w $H_2O \equiv 0.48$ mol H_2O

Similarly prepared was:-

Example 10

4-Methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(2-pyridinyl)phenyl] benzamide as an off-white solid (0.22g), m.p. 154-155°C.

Analysis Found: C,71.45; H,6.7; N,13.7.

$C_{24}H_{26}N_4O_2$ 0.05 CH_3CH_2OH 0.05 $CH_3CO_2C_2H_5$ requires

C,71.3; H,6.6; N,13.7%

From Intermediate 7 (0.3g) and 2-bromopyridine (156µl). Purification by SPC eluting with System A (96:4:0.4) afforded the title compound.

Example 11

2-Methoxy-5-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl]benzamide

A mixture of Intermediate 17 (1.1g) and sodium hydroxide (574mg) in aqueous methanol (45ml) was heated at reflux for 2.5h, under nitrogen. The pH was adjusted to 1 with 2N hydrochloric acid (15ml) and the solvents evaporated in vacuo to yield a white solid (2.013g). A portion of the solid (1.01g) was dissolved in dry pyridine (20ml), cooled to 0°C, and thionyl chloride (0.131ml) was added dropwise to the stirred solution. Stirring was continued at 0°C for 1h, 4-(4-pyridinyl)benzenamine was added and the reaction stirred at 20°C, under nitrogen, for 72h, then heated at 50°C for 2h. The pyridine was evaporated in vacuo to give a yellow solid which was added to 8% sodium bicarbonate (75ml) and extracted with dichloromethane (3 x 100ml). The dried extracts were evaporated in vacuo to yield a cream solid. This was preabsorbed onto silica (Merck 7734) and purified by FCC eluting with System A (250:8:1) to give 98mg of impure material. This was chromatographed on silica (Merck 7729) eluting with the same solvent to give the title compound as a white crystalline solid (46mg) m.p. 171-172.5°C.

T.l.c. System A (100:8:1) Rf 0.54.

Similarly prepared was :-

Example 12

2-Hydroxy-5-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl]-benzamide as a yellow solid (100mg) m.p. 236-240^{0}C.

Assay Found : C,66.85; H,6.45; N,13.60;

$C_{23}H_{24}N_4O_2.1.8H_2O$ requires C,65.65; H,6.60; N,13.30%

Water determination 7.84% H_2O w/w ≡ 1.8mol H_2O.

From Intermediate 18 (650mg) and 4-(4-pyridinyl)benzenamine (378mg). Purification by FCC eluting with System A (100:8:1) followed by trituration from ether (40ml) and further FCC eluting with System A (50:8:1) afforded the title compound.

Example 13

4,5-Dimethoxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl]benzamide

Intermediate 16 (272mg) was heated to reflux in 1:1 aqueous methanol (15ml) containing sodium hydroxide (161mg) for 2h. The mixture was allowed to cool and was acidified (pH1) with 2N HCl. Evaporation gave an off-white solid which was dried in vacuo for 18h. This was then suspended in dry pyridine (10ml) and cooled (0^o) and then treated with thionyl chloride (0.07ml). Stirring was continued at 0^o for 1h then at 20^o for 1h. 4-(4-Pyridinyl)benzeneamine (138mg) was then added and the mixture heated to 70^o for 18h. The pyridine was evaporated and the residue purified by FCC eluting with System A (200:8:1) to give the title compound as a fawn-coloured solid (179mg) m.p. 207-210^o (dec.)

Assay Found: C,68.4; H,6.7; N,12.5;

$C_{25}H_{28}N_4O_3.0.2C_2H_6O.0.05H_2O$ requires C,68.9; H,6.65; N,12.65%

Water Determination 0.21% w/w = 0.05mol% H_2O

Example 14

2-Methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl] benzamide

A mixture of Intermediate 15 (1.5g crude) in thionyl chloride (10ml) was refluxed for 2h and evaporated. The residue was dissolved in THF (10ml) and treated with a solution of 4-(4-pyridinyl)benzenamine (0.3g) and sodium hydroxide (200mg) in

THF (5ml) and water (5ml) in one portion. The orange solution was stirred for 30min, diluted with water (50ml) and extracted with dichloromethane (3x50ml). The dried extract was evaporated and the residue was purified by FCC eluting with System B (485:15:1.5) to give the title compound as a white solid (350mg), m.p. 132-133°.

T.l.c. System B (90:10:1), Rf 0.5.

Example 15

2-Hydroxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl)phenyl]benzamide

A mixture of the product of Example 14 (150mg) and pyridine hydrochloride (330mg) was heated at ~180° for 6h. Sublimed pyridine hydrochloride was scraped from the flask back into the reaction mixture several times during the heating. The cooled mixture was treated with aqueous sodium hydroxide (2N; 50ml) and dichloromethane (2x50ml). The resultant brown gum was dissolved in methanol and retained. The sodium hydroxide phase was neutralised with hydrochloric acid and extracted with dichloromethane (2x50ml). The second dichloromethane extract was combined with the methanol phase and the dried mixture was evaporated. The residue was purified on a column of silica eluting with System B (240:10:1) to give the title compound as a white foam (75mg).

T.l.c. System B (90:10:1), Rf 0.4

Analysis Found:	C,70.3; H,6.2; N,14.0;
$C_{23}H_{24}N_4O_2.0.2H_2O$ requires	C,70.4; H,6.3; N,14.3%

Example 16

4-Methoxy-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide

A mixture of Intermediate 24 (150mg), Intermediate 7 (219mg), sodium carbonate (207mg) and tetrakis(triphenylphosphine)palladium (0) (13mg) in 1:1 aqueous DME (20ml) was heated at reflux under nitrogen for 18h. The cooled mixture was evaporated onto silica gel (~5g) and the residue chromatographed on silica gel eluting with System A (200:8:1) to give the title compound as colourless foam (173mg).

T.l.c. System A (100:8:1) Rf 0.40

Assay Found:- C,66.65; H,6.2; N,13.05;
$C_{29}H_{31}N_5O_3.1.5H_2O$ requires :- C,66.4; H,6.5; N,13.35%.

Similarly prepared was: -

Example 17
4-Methoxy-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide as a colourless foam (370mg).
T.l.c. System A (100:8:1) Rf 0.58
Assay Found C,67.8; H,6.35; N,13.25;
$C_{29}N_{31}N_5O_3.0.3H_2O.0.7C_2H_6O$ requires C,68.2; H,6.75; N,13.1%
Water Determination Found 1.15% w/w ≡ 0.3mol % H_2O
From a mixture of Intermediate 7 (430mg), Intermediate 21 (268mg) in aqueous DME (1:1, 30ml) containing sodium carbonate (370mg) and tetrakis(triphenylphosphine)palladium (0) (24mg).

Example 18
4-Chloro-N-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide
A suspension of Intermediate 11 (150mg) and Intermediate 24 (116mg) in DME (4ml) and 2N sodium carbonate (1ml) was treated with tetrakis(triphenylphosphine)palladium (0) (20mg) under nitrogen. The resulting mixture was heated to reflux for 10 hours. The reaction mixture was cooled to room temperature, added to water (20ml) and sodium carbonate (5ml;2N), and extracted with dichloromethane (2x25ml). The combined, dried organic extracts were concentrated in vacuo to give a foam which was purified by FCC eluting with System A (300:8:1) to give the title compound as a white foam (65mg).
T.l.c. System A (100:8:1) Rf 0.65
n.m.r. ($CDCl_3$) δ 2.38 (6H,2xs), 2.64 (7H, m+s), 3.18 (4H,m), 7.3-8.0 (10H,m).

The following examples illustrate pharmaceutical formulations according to the invention. The term "active ingredient" is used herein to represent a compound of formula (I).

Pharmaceutical Example 1

Oral Tablet A	
Active Ingredient	700mg
Sodium starch glycollate	10mg
Microcrystalline cellulose	50mg
Magnesium stearate	4mg

Sieve the active ingredient and microcrystalline cellulose through a 40 mesh screen and blend in a appropriate blender. Sieve the sodium starch glycollate and magnesium stearate through a 60 mesh screen, add to the powder blend and blend until homogeneous. Compress with appropriate punches in an automatic tablet press. The tablets may be coated with a thin polymer coat applied by the film coating techniques well known to those skilled in the art. Pigments may be incorporated in the film coat.

Pharmaceutical Example 2

Oral Tablet B	
Active Ingredient	500mg
Lactose	100mg
Maize Starch	50mg
Polyvinyl pyrrolidone	3mg
Sodium starch glycollate	10mg
Magnesium stearate	4mg
Tablet Weight	667mg

Sieve the active ingredient, lactose and maize starch through a 40 mesh screen and blend the powders in a suitable blender. Make an aqueous solution of the polyvinyl pyrrolidone (5 - 10% w/v). Add this solution to the blended powders and mix until granulated; pass the granulate through a 12 mesh screen and dry the granules in a suitable oven or fluid bed dryer. Sieve the remaining components

through a 60 mesh screen and blend them with the dried granules. Compress, using appropriate punches, on an automatic tablet press.

The tablets may be coated with a thin polymer coat applied by film coating techniques well known to those skilled in art. Pigments may be incorporated in the film coat.

Pharmaceutical Example 3

Inhalation Cartridge	
Active Ingredient	1mg
Lactose	24mg

Blend active ingredient, particle size reduced to a very fine particle size (weight mean diameter ca. 5µm) with the lactose in a suitable powder blender and fill the powder blender into No. 3 hard gelatin capsules.

The contents of the cartridges may be administered using a powder inhaler.

Pharmaceutical Example 4

Injection Formulation

	% w/v
Active ingredient	1.00
Water for injections B.P. to	100.00

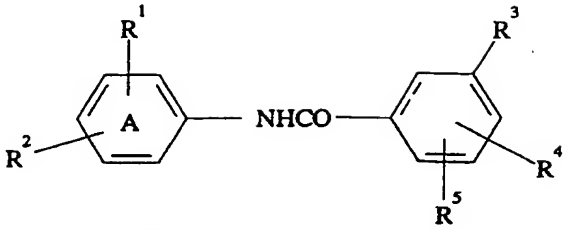
Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the active ingredient using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included.

The solution is prepared, clarified and filled into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by

filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen.

CLAIMS

A compound of formula (I):



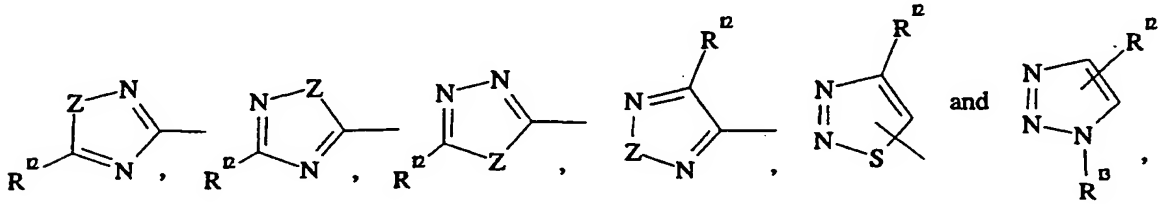
(I)

or a salt or solvate (eg hydrate) thereof, in which

R^1 represents H, F, Cl, Br, I, C_{1-6}alkyl or C_{1-6}alkoxy;

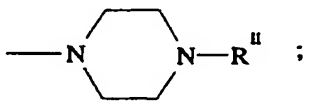
R^2 represents a phenyl or pyridyl group optionally substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkyl (optionally substituted by hydroxy), C_{1-6}alkoxy, hydroxy, $-CF_3$, -CN, $-NO_2$, $-CO_2R^{10}$, $-COR^6$, $-SR^6$, $-SOR^6$, $-SO_2R^6$, $-CR^6{=}NOR^7$, $-CONR^6R^7$, $-CONR^6(CH_2)_mCO_2R^7$, $-CONR^6(CH_2)_mOC_{1-4}$alkyl, $-SO_2NR^6R^7$, $-OC(O)NR^6R^7$, $-(CH_2)_nNR^8R^9$, $-(CH_2)_nOC(O)C_{1-4}$alkyl or C_{1-4}alkoxyalkyl (optionally substituted by C_{1-4}alkoxy or hydroxy); or

R^2 represents a phenyl group substituted by a group selected from



and optionally further substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy and C_{1-6}alkyl ;

R^3 represents the group



R^4 and R^5, which may be the same or different, each independently represent H, F, Cl, Br, I, hydroxy, C_{1-6}alkoxy or C_{1-6}alkyl;
R^6, R^7 and R^8, which may be the same or different, each independently represent H or C_{1-6}alkyl ;
or $-NR^6R^7$ forms a saturated heterocyclic ring which has 4, 5 or 6 ring members, and optionally contains in the ring one oxygen or sulphur atom;
R^9 represents H, C_{1-6}alkyl, $-COR^{16}$ or $-SO_2R^{17}$;
or $-NR^8R^9$ forms a saturated heterocyclic ring which has 4, 5 or 6 ring members and optionally contains in the ring one oxygen or sulphur atom and may optionally be substituted by an oxo group;
R^{10} represents H, or C_{1-6}alkyl optionally substituted by one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy or $-NR^6R^7$;
R^{12} represents H, $-NR^{14}R^{15}$ or a C_{1-6}alkyl group optionally substituted by one or two substituents selected from C_{1-6}alkoxy, hydroxy and C_{1-6}acyloxy;
R^{11}, R^{13} and R^{14}, which may be the same or different, each independently represent H, or C_{1-6}alkyl;
R^{15} represents H C_{1-6}alkyl, C_{1-6}acyl, benzoyl or $-SO_2R^{18}$;
R^{16} represents H, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-4}alkoxyalkyl;
R^{17} represents C_{1-6}alkyl or phenyl;
R^{18} represents C_{1-6}alkyl or phenyl ;
Z represents an oxygen atom or a group selected from NR^{13} and $S(O)_k$; and
k represents zero, 1 or 2.

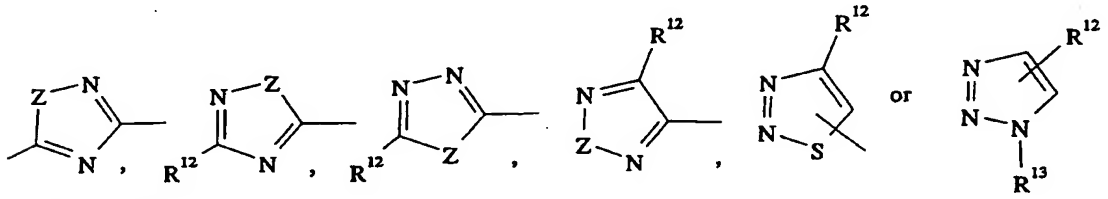
2. A compound as claimed in Claim 1 wherein R^1 is attached at a position ortho to the group R^2 on the phenyl ring A in general formula (I).

3. A compound as claimed in Claim 1 or Claim 2 wherein R^1 represents H or methyl.

4. A compound as claimed in any preceding claim wherein R^2 is attached at the meta or the para position of the phenyl ring designated A in formula (I) above, relative to the amide linkage.

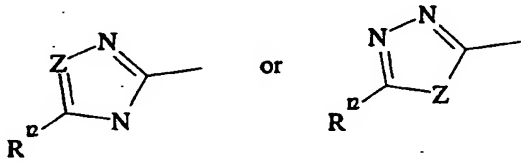
5. A compound as claimed in any preceding claim wherein R^2 is a 3-pyridyl or 4-pyridyl group optionally substituted by C_{1-6}alkyl.

6. A compound as claimed in any of Claims 1 to 4 wherein R^2 represents phenyl substituted by a substituent of formula



in the position para to the phenyl ring A, and optionally substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy or C_{1-6}alkyl, which is (are) attached at a position ortho to the phenyl ring A in general formula (I).

7. A compound as claimed in any of Claims 1 to 4 and 6 wherein R^2 represents a phenyl group substituted by the substituent



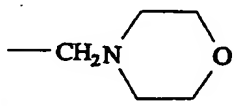
and optionally further substituted by one or two substituents selected from F, Cl, Br, I, C_{1-6}alkoxy, hydroxy or C_{1-6}alkyl.

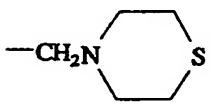
8. A compound as claimed in Claim 7 wherein Z represents an oxygen atom.

9. A compound as claimed in any of Claims 1 to 4 wherein R^2 represents a phenyl group optionally substituted by one or two substituents selected from a halogen atom; a C_{1-6}alkyl group optionally substituted by a hydroxy group; hydroxy; -CN; $-COR^6$ where R^6 is C_{1-6}alkyl; $-SR^6$ where R^6 is C_{1-6}alkyl; $-SOR^6$ where R^6 is a C_{1-6}alkyl; $-CR^6{=}NOR^7$ where R^6 is H or C_{1-6}alkyl, and R^7

is H or C_{1-6}alkyl -$CONR^6R^7$ where R^6 and R^7 each independently represent C_{1-6}alkyl, or -NR^6R^7 forms a saturated heterocyclic group which has six members and contains in the ring one oxygen atom; -$CONR^6(CH_2)_mOC_{1-4}$alkyl, where R^6 is C_{1-6}alkyl, and m is two, -$SO_2NR^6R^7$ where R^6 and R^7 each independently represent a H or C_{1-6}alkyl; -$OC(O)NR^6R^7$ where R^6 and R^7 each independently represent C_{1-6}alkyl; -$(CH_2)_nNR^8R^9$ where R^8 is H or C_{1-6}alkyl, R^9 is C_{1-6}alkyl or -COR^{12} (where R^{12} is C_{1-6}alkyl, C_{1-6}alkoxy, or C_{1-4}alkoxyalkyl) or -SO_2R^{13} (where R^{13} is C_{1-6}alkyl) or -NR^8R^9 forms a saturated heterocyclic group which has six ring members and contains in the ring one oxygen or sulphur atom, and n is zero, 1 or 2; or C_{1-4}alkoxyalkyl substituted by C_{1-4}alkoxy .

10. A compound as claimed in Claim 9 wherein R^2 represents a phenyl group substituted by a group selected from hydroxymethyl, hydroxy, -$COCH_3$, -$SOCH_3$, -$C(CH_3)$=NOH, -$CON(CH_3)_2$, -SO_2NH_2, -SO_2NHCH_3, -$SO_2N(CH_3)_2$, -$OC(O)N(CH_3)_2$, -$NHCH_3$, -$N(CH_3)_2$, -$N(CH_3)COCH_3$, -$CH_2NHCO_2CH_2CH_3$, -$CH_2N(CH_3)COCH_2OCH_3$, -$NHSO_2CH_3$,



,


or $CH_2OCH_2CH_2OCH_3$.

and optionally further substituted by a chlorine atom or a methyl group

11. A compound selected from

N-(4'-hydroxy[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide;

2-chloro-4'-[[4-methoxy-3-(4-methyl-1-piperazinyl)benzoyl]amino][1,1'-biphenyl]-4-carboxamide;

N-(4'-acetyl-2'-methyl-[1,1'-biphenyl]-4-yl)-4-methoxy-3-(4-methyl-1-piperazinyl)benzamide;

4'-[[4-chloro-3-(4-methyl-1-piperazinyl)benzoyl]amino]-2-chloro-N,N-dimethyl[1,1'-biphenyl]-4-carboxamide;

4-methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl) phenyl]benzamide;

4-methoxy-3-(4-methyl-1-piperazinyl)-N-[4-(3-pyridinyl) phenyl]benzamide;

2-methoxy-5-(4-methyl-1-piperazinyl)-N-[4-(4-pyridinyl) phenyl]benzamide;
and their physiologically acceptable salts and solvates.

4-methoxy-N-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;

4-methoxy-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;

4-chloro-N-[2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)[1,1'-biphenyl]-4-yl]-3-(4-methyl-1-piperazinyl)benzamide;
and their physiologically acceptable salts and solvates.

12. A compound as claimed in any preceding claim for use in therapy.

13. A pharmaceutical composition comprising a compound as claimed in any of Claims 1 to 11 and a pharmaceutically acceptable carrier therefor.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (ie Search report)	Application number GB 9325842.4
Relevant Technical Fields (i) UK Cl (Ed.) (ii) Int Cl (Ed.5) C07D 295/08	Search Examiner MISS D DAVIES Date of completion of Search 9 FEBRUARY 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: CAS-ONLINE, EDOC	Documents considered relevant following a search in respect of Claims :- 1-13

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Category	Identity of document and relevant passages	Relevant to claim(s)
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